Albumin Versus Balanced Crystalloid for the Early Resuscitation of Sepsis: An Open Parallel-Group Randomized Feasibility Trial. The ABC-Sepsis Trial

OBJECTIVES: International guidelines recommend IV crystalloid as the primary fluid for sepsis resuscitation, with 5% human albumin solution (HAS) as the second line. However, it is unclear which fluid has superior clinical effectiveness. We conducted a trial to assess the feasibility of delivering a randomized controlled trial comparing balanced crystalloid against 5% HAS as sole early resuscitation fluid in patients with sepsis presenting to hospital.

DESIGN: Multicenter, open, parallel-group randomized feasibility trial.

SETTING: Emergency departments (EDs) in 15 U.K. National Health Service (NHS) hospitals.

PATIENTS: Adult patients with sepsis and a National Early Warning Score 2 greater than or equal to five requiring IV fluids withing one hour of randomization.

INTERVENTIONS: IV fluid resuscitation with balanced crystalloid or 5% HAS for the first 6 hours following randomization.

MEASUREMENTS AND MAIN RESULTS: Primary feasibility outcomes were recruitment rate and 30-day mortality. We successfully recruited 301 participants over 12 months. Mean (SD) age was 69 years (± 16 yr), and 151 (50%) were male. From 1303 participants screened; 502 participants were potentially eligible and 300 randomized to receive trial intervention with greater than 95% of participants receiving the intervention. The median number of participants per site was 19 (range, 1–63). Thirty-day mortality was 17.9% ($n = 53$). Thirty-one participants died (21.1%) within 30 days in the 5% HAS arm, compared with 22 participants (14.8%) in the crystalloid arm (adjusted odds ratio, 1.50; 95% CIs, 0.84–2.83).

CONCLUSIONS: Our results suggest it is feasible to recruit critically ill patients to a fluid resuscitation trial in U.K. EDs using 5% HAS as a primary resuscitation fluid. There was lower mortality in the balanced crystalloid arm. Given these findings, a definitive trial is likely to be deliverable, but the point estimates suggest such a trial would be unlikely to demonstrate a significant benefit from using 5% HAS as a primary resuscitation fluid in sepsis.

KEYWORDS: albumin; fluids; randomized controlled trial; resuscitation; sepsis

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Sepsis, defined as "life-threatening organ dysfunction caused by a dysregulated host response to infection" (1), is common and associated with significant mortality. In the United Kingdom, patients with sepsis presenting to the emergency department (ED) with a National Early Warning Score (NEWS) greater than or equal to 5 (2), have an in-hospital mortality of ~20% (3–5).

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KEY POINTS

Question: Is it feasible to deliver a randomized controlled trial comparing balanced crystalloid with 5% human albumin solution as fluid resuscitation in patients presenting to the emergency department with sepsis?

Findings: We demonstrated the feasibility of delivering such a trial in a multicenter setting over the course of 12 months. Although there was a lower mortality in the balanced crystalloid arm, the trial was not powered to answer this question.

Meaning: A definitive trial is likely to be deliverable but is unlikely to demonstrate that 5% human albumin solution confers a survival advantage over balanced crystalloid that is clinically important.

IV fluids are often prescribed during the resuscitation of patients with sepsis to increase circulating volume, maintain mean arterial blood pressure, and support end-organ perfusion. Current international guidelines recommend crystalloids as the first choice for initial resuscitation and 5% human albumin solution (HAS) as the second line, where large volume resuscitation is required (6, 7). However, there is uncertainty around the best choice of IV fluid for ED management of patients with sepsis. Evidence from critical care settings suggest marginal benefit with HAS for adult critically ill patients with septic shock, but this evidence may not be extrapolatable for early fluid resuscitation in the ED population (8–12). Patients admitted to critical care with sepsis may differ from those presenting to the ED. Patients tend to be younger, more severely unwell and with different reasons for infection e.g. post-operative. Additionally, they are at a different time point in the resuscitation treatment pathway and disease progression. Lastly, there are ED patients with sepsis who may not be admitted to critical care due to treatment escalation decisions.

In this context, we conducted a randomized controlled trial comparing 5% HAS with balanced crystalloid for the early resuscitation of adults with community-acquired sepsis and a NEWS 2 greater than or equal to 5 in the ED. Our aims were to assess the feasibility of recruiting in this ED setting, test adherence to the trial protocol, and ascertain outcome events to inform a future effectiveness trial.

METHODS

Design

The ABC-Sepsis trial was a prospective two-armed, open, parallel-group, randomized feasibility trial in adults with suspected or confirmed community acquired sepsis. The trial was registered prospectively (https://clinicaltrials.gov/show/NCT04540094; EudraCT Number 2020-013520-18) and the trial protocol has been reported previously (13). The trial was investigator-led, with oversight delivered by a trial management group in conjunction with independent trial steering and data monitoring committees. The "Feasibility of 5% Albumin Compared With Balanced Crystalloid, as Intravenous Fluid Resuscitation in Adult Patients With Sepsis, Presenting as an Emergency to Hospital (ABC Sepsis)" trial was approved by the South East Scotland Research Ethics Committee 01 (REC:20/SS/0110) on December 11, 2020. The trial was delivered in accordance with the ethical standards of this regional ethical committee and with the Helsinki Declaration of 1975. The trial was coordinated by the Edinburgh Clinical Trials Unit (ECTU) with governance and monitoring provided by the Academic and Clinical Central Office for Research and Development on behalf of the trial sponsors (University of Edinburgh and NHS Lothian). The article is reported in line with the 2010 Consolidated Standards of Reporting Trials (CONSORT) statement extension for feasibility trials. This article was written, reviewed, and agreed by the authors who had full access to the data and vouch for the accuracy and completeness of all data and for the fidelity of the trial to the protocol.

Setting

Participants were recruited in EDs and Medical and Surgical Admissions Units in 15 U.K. National Health Service (NHS) hospitals between June 01, 2021, and June 06, 2022.

Screening and Eligibility

Patients with suspected sepsis were identified, screened for eligibility, and approached for informed consent within 12 hours of presentation to hospital by appropriately trained and delegated research nurses or members of the clinical team. Eligibility was determined by the following criteria: 1) clinically suspected or proven

infection as the primary reason for hospital attendance; 2) NEWS 2 greater than or equal to 5; and 3) the treating clinician determined that IV fluid resuscitation was required to be commenced within 1 hour of assessment. Details of full inclusion and exclusion criteria are provided in **Supplementary Table S1** (http://links.lww.com/CCM/H557). The NEWS 2 score is a track and trigger scoring system using respiratory rate, oxygen saturation, need for oxygen therapy, heart rate, blood pressure, level of consciousness/confusion, and temperature with higher numbers associated with severity of illness and risk of deterioration. It is the nationally adopted early warning score used in the NHS in the United Kingdom (2).

Consent, Randomization, and Blinding

A hierarchal consent process was used as detailed in the protocol (13). Briefly, if participants had capacity, they were recruited by written or verbal (witnessed) consent. If this was not possible, we approached personal or professional legal representative for consent. If none of these options were available within 30 minutes, deferred consent from a delegated clinician was provided given the requirement for emergency treatment. At the earliest possible time point, after the patient had regained capacity they were provided trial information and consent was requested (**Supplementary fig. S1**, http://links.lww.com/CCM/H557). Randomization was completed using a web-based randomization service (managed by ECTU) to ensure allocation concealment. After confirmation of trial eligibility and consent, patients were randomized on a 1:1 basis to 5% HAS or balanced crystalloid in addition to standard care with stratification by age (< 70 and ≥ 70 yr old), serum lactate (< 2 and ≥ 2 mmol/L), and study site. This was an open trial with the treating clinician and participant being aware of the trial allocation. The central team was blinded to trial allocation and outcomes.

Intervention

After randomization, the allocated IV fluid was started as soon as possible. If participants were receiving either fluid before randomization and were allocated the alternative fluid, the pre-randomization fluid was stopped. The protocol stated that in the first 6 hours following randomization, no other IV fluid apart from the trial allocation should be administered for resuscitation. Details of guidance around IV fluid delivery are provided in the trial protocol (13).

Outcomes

There were two trial primary feasibility outcomes: 1) recruitment rate (two participants per site per month across 15 centers) and 2) 30-day mortality. The secondary outcomes including hospital length of stay (LOS), length of critical care stay (ICU LOS), protocol adherence, fluid volume, and safety are detailed in **Supplementary Table S2** (http://links.lww.com/CCM/H557). In the first 50 participants, there was an additional exploratory health economic outcome up to 180 days.

Data Collection and Follow-Up

Data were collected from consent until final follow-up at 90 days (**Supplementary Table S3**, http://links.lww.com/CCM/H557). The first 50 participants were followed up for 180 days. There was no further in-person follow-up as study data, including outcomes, were assessed using medical records, apart from the first 50 participants who had a questionnaire assessing quality of life measures posted to them with telephone follow-up of non-responders by members of the recruiting site research team. Study data were collected and managed using Research Electronic Data Capture (14, 15).

Sample Size

As a feasibility trial, no formal sample size estimate was determined. Our pragmatic sample size of 300 was based on projected recruitment of ~two participants per month, over a 12 months recruitment period in approximately 15 centers. It was anticipated this would provide sufficient data to enable assessment of protocol fidelity and feasibility, and number of outcome events to inform design of a fully powered trial.

Statistical Analysis

The predefined trial Statistical Analysis Plan is available at: https://www.ed.ac.uk/usher/edinburgh-clinical-trials/our-studies/all-current-studies/abc-sepsis. The primary feasibility outcome of recruitment was the proportion of those screened who were randomized. The 30-day mortality outcome was summarized by randomized treatment group and then analyzed using a mixed-effects logistic regression adjusting for site

and prespecified prognostic baseline covariates (age, active cancer, and heart failure). Predefined exploratory subgroup analyses on the 30-day mortality outcome were severity of illness at recruitment (NEWS 2, quick Sequential Organ Failure Assessment [qSOFA], and lactate), age, pre-existing known heart failure, pre-existent chronic kidney disease, and baseline albumin.

We aimed to demonstrate the feasibility of collecting relevant data to enable health economic analysis for a future trial, for example, length of hospital stay and hospital readmission. Health-related quality of life (HRQoL) was captured for the first 50 recruited patients using the EuroQOL-5 Dimensions- 5 Levels (EQ-5D-5L) at baseline, 7 days, and 180 days (16). Baseline values were obtained by proxy or by recall where necessary.

RESULTS

Participants

We recruited 301 participants, with 300 participants available for analysis; a single participant withdrew before treatment allocation. The mean (SD) age of participants was 69 years (± 16 yr), and 151 (50%) were male. The median (interquartile range [IQR]) NEWS 2 score was 8 (6–10); 46 participants (15%) had a lactate greater than 2 mmol/L and systolic blood pressure less than 90 mm Hg or mean arterial pressure less than 65 mm Hg. The commonest presumed site of infection was the respiratory tract (n = 182 [61%]) (**Table 1**). Participants were similar between treatment allocations at randomization (Table 1: baseline characteristics including severity of illness, infection source, antibiotic timing, and prescription); (**Fig. 1**: CONSORT diagram); **Supplementary Table S4** (http://links.lww.com/CCM/H557: comorbidities and laboratory results); and **Supplementary Table S5** (http://links.lww.com/CCM/H557: microbiological sampling).

Primary Feasibility Outcomes

Recruitment. One thousand three hundred three participants were screened; 502 participants were eligible and 300 were randomized and received the allocated intervention. The reasons for not recruiting screened patients are described in Figure 1. Once active recruitment began, the trial recruited to time and target (for trial recruitment by month, **Supplementary fig. S2**, http://links.lww.com/CCM/H557). The median number of participants recruited by site was 19 (range, 1–63). The mean number of participants per site per recruitment month was 2.4 participants with a median of 1.9 participants per site per recruitment month.

Thirty-Day Mortality. Overall, 30-day mortality was 17.9% (n = 53). Thirty-one of 147 participants (21.1%) died within 30 days in the 5% HAS arm, compared with 22 of 149 participants (14.8%) in the balanced crystalloid arm (adjusted odds ratio, 1.50; 95% CIs, 0.84–2.83) (**Table 2**). Prespecified subgroup analyses for 30-day mortality for the following: age, sex, NEWS 2, qSOFA, lactate, albumin, critical care admission, chronic kidney disease, and heart failure are reported in **Supplementary Table S6** (http://links.lww.com/CCM/H557) with the treatment effect consistent across subgroups.

Secondary Outcomes

Protocol Adherence. One hundred seventy-two participants (57%) received IV fluid prior to randomization; with a median volume of 100 mL (IQR, 0–500 mL) in the 5% HAS arm and 200 mL (IQR, 0–500 mL) in the balanced crystalloid (**Table 3**). Two hundred eighty-seven participants (96%) received the allocated IV resuscitation fluid for resuscitation in the first 6 hours after randomization; 146 (97%) in the 5% HAS arm and 141 (94%) in the balanced crystalloid arm. The median volume of the allocated fluid administered to participants in the first 6 hours was 750 mL (IQR, 500–1400 mL) in the 5% HAS arm and 1250 mL (IQR, 1000–2000 mL) in the balanced crystalloid arm (Table 3). In the first 6 hours after randomization, 33 participants (22%) in the 5% HAS arm received crossover (defined as balanced crystalloid in the 5% HAS arm or 5% HAS in the balanced crystalloid arm administered for resuscitation purposes) IV fluid for resuscitation compared with 1 (1%) in the balanced crystalloid arm. The median volume of total IV fluid (allocated, crossover, and other) administered to participants in the first 6 hours was 1100 mL (IQR, 600–1600 mL) in the 5% HAS arm and 1358 mL (IQR, 1000–2069 mL) in the balanced crystalloid arm (Table 3). **Figure 2** details the trial allocated, and total IV fluid by arm delivered in the first 6 hours; and **Supplementary fig. S3** (http://links.lww.com/CCM/H557) demonstrates the proportion of participants receiving, and the volume of crossover IV fluid. The median (mL/kg) of trial allocated IV fluid administered in the first 6 hours was 10 mL/kg (IQR, 6–18 mL/kg) in the 5% HAS arm compared with 17.7 mL/kg (IQR, 12–26 mL/kg) in the balanced crystalloid (Table 3).

TABLE 1.
Baseline Characteristics

Baseline Characteristics	5% Human Albumin Solution (*n* = 150)	Balanced Crystalloid (*n* = 150)	All
Sex, *n* (%)			
Male	71 (47)	80 (53)	151
Female	79 (53)	70 (47)	149
Age (yr), mean (SD)	70 (15)	69 (17)	69 (16)
Time from hospital arrival to randomization (min), median (IQR)	72 (46–116)	71.5 (49–99)	72.0 (46.5–111)
Time from hospital arrival to treatment allocation (min), median (IQR)	88 (60–144)	84 (55–129)	87.0 (57–136)
Baseline vital signs			
Pulse (beats/min), median (IQR)	111 (96–121)	109 (95–127)	110 (95–125)
Respiratory rate (breaths/min), median (IQR)	24 (21–28)	24 (21–27)	24 (21–28)
Temperature (°C), median (IQR)	37.7 (36.6–38.7)	37.7 (36.9–38.6)	37.7 (36.7–38.7)
Systolic blood pressure (mm Hg), median (IQR)	110 (93–136)	110 (93–130)	110 (93–133)
Oxygen saturation (%), median (IQR)	95 (93–97)	95 (93–97)	95 (93–97)
Lactate (mmol/L), median (IQR)	2.2 (1.4–3.6)	2.1 (1.4–3.8)	2.2 (1.4–3.7)
Quick Sequential Organ Failure Assessment 2–3, *n* (%)	58 (38.7)	67 (45.6)	125 (42.1)
Presumed site of infection, *n* (%)			
Chest	95 (63)	87 (58)	182 (60)
Urine	16 (11)	33 (22)	49 (16)
CNS	1 (1)	0	1 (1)
Skin	9 (6)	2 (1)	11 (4)
Abdomen	13 (9)	9 (6)	22 (7)
Unknown	12 (8)	10 (7)	22 (7)
Other	3 (2)	9 (6)	12 (4)
Antibiotic administration			
Antibiotics administered during index presentation, *n* (%)	145 (97.3)	148 (98.7)	293 (98.0)
Antibiotics administered before randomization, *n* (%)	80 (55.2)	87 (59.2)	167 (57.2)
Time of hospital presentation to antibiotics (first dose, min), median (IQR)	65 (41–106)	67 (40–99)	66.0 (40–102)

IQR = interquartile range.

Supplementary Table S7 and **Supplementary figure S4** (http://links.lww.com/CCM/H557) detail the allocated, and total IV fluid volumes (mL) and mL/kg, delivered in the first 24 hours.

Other Secondary Outcomes. Overall, 293 participants (98%) received antibiotics with 167 participants (57.2%) receiving these before randomization (Table 1).

Comparative rates of critical care interventions including IV vasopressor administration, invasive ventilation, and renal replacement therapy are described in **Table 4**. The rates of acute kidney injury, pulmonary edema, and anaphylaxis are detailed in Table 4. The event rates for critical care interventions and recognized complications were consistently lower in the balanced crystalloid arm.

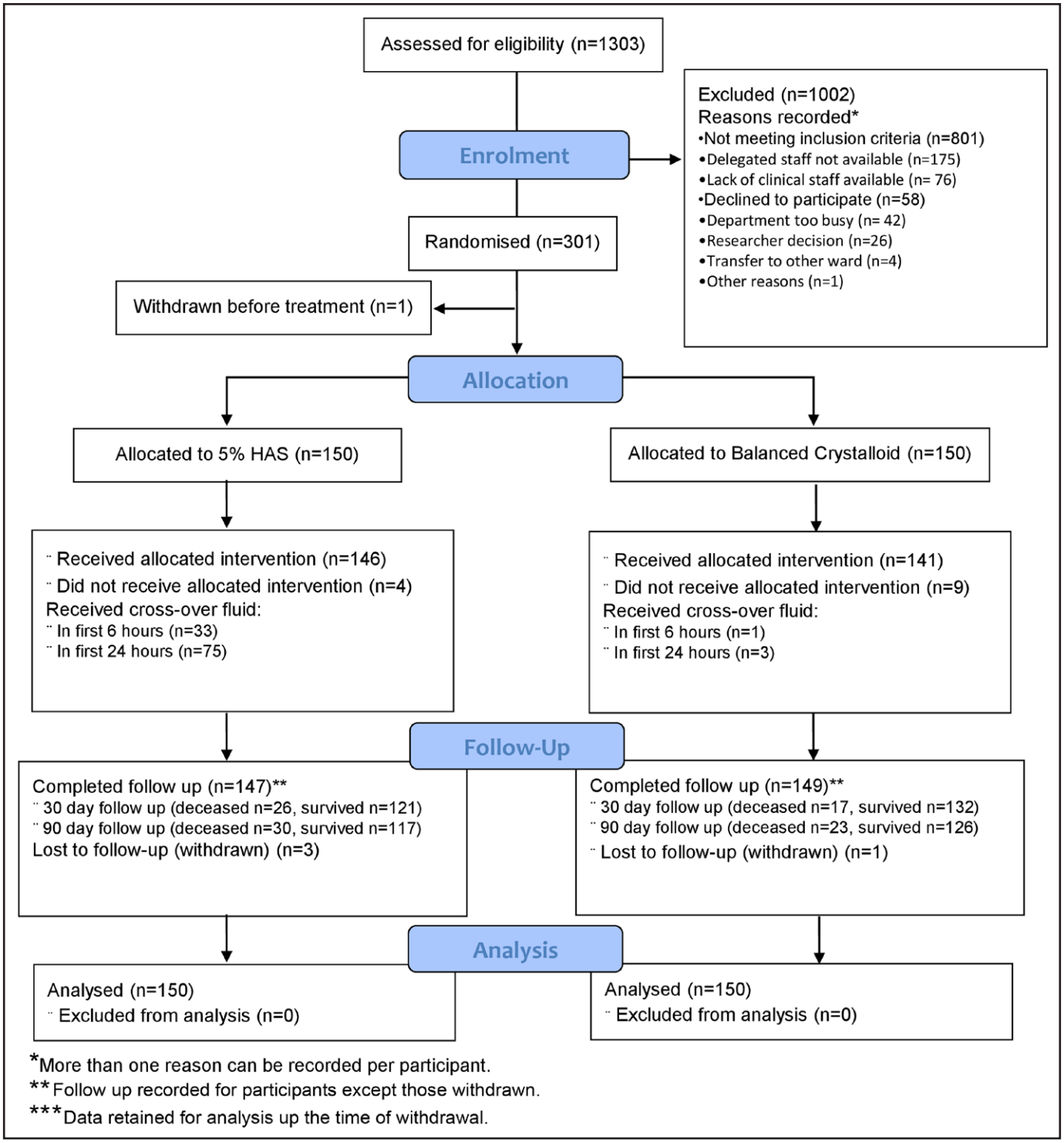

Figure 1. ABC-Sepsis trial. Consolidated Standards of Reporting Trials diagram. HAS = human albumin solution.

Among the 147 participants allocated to 5% HAS, 29 died in-hospital (19.5%), compared with 23 of 149 participants (15.4%) in the balanced crystalloid arm. In the 5% HAS arm, 43 died (29.3%) within 90 days, compared with 32 (21.5%) in the balanced crystalloid arm (Table 2).

The median length of hospital stay was 6 days (IQR, 4–13 d) in the 5% HAS group compared with 6 days (IQR, 3–14 d) in the balanced crystalloid group during index hospitalization (Table 4). Only 39 participants (13%) were admitted to critical care during index hospitalization (22 [15%] 5% HAS group compared with 17 [11%] balanced crystalloid group). Seventy participants were readmitted to hospital within 90 days of randomization, 38

TABLE 2.
Primary and Other Mortality Outcomes

Outcomes	5% Human Albumin Solution (*n* = 147)	Balanced Crystalloid (*n* = 149)	Total (*n* = 296)	OR[a] (95% CI)
Primary outcome, *n* (%)				
Mortality at 30 d	31 (21.1)	22 (14.8)	53 (17.9)	1.54 (0.84–2.83)
Other mortality outcomes, *n* (%)				
In-hospital mortality (index admission)	29 (19.5)	23 (15.4)	52 (17.4)	
90-d mortality	43 (29.3)	32 (21.5)	75 (25.3)	

OR = odds ratio.
[a]Adjusted for site (as random effect) and baseline covariates known to be strong predictors of 30-d mortality (age, active cancer, and heart failure).

TABLE 3.
IV Fluid During Intervention Period (0–6 hr)

IV Fluid Characteristics	5% Human Albumin Solution	Balanced Crystalloid	All
Received IV fluid before randomization			
n (%)	83 (55)	89 (59)	172 (57)
Time between initial IV fluid and randomization (min)			
Median (IQR)	41 (17–76)	36 (17–63)	37 (17–70)
n	149	150	299
Total volume of IV fluid before randomization (mL)			
Median (IQR)	100 (0–500)	200 (0–500)	100 (0–500)
n	150	150	300
Volume of intervention[a] IV fluid in first 6 hr (mL)			
Median (IQR)	750 (500–1400)	1250 (1000–2000)	1000 (500–1720)
n	147	144	291
Crossover[b] fluid in first 6 hr (mL)			
Median (IQR)	500 (250–625)	750 (0)	500 (250–656)
n	33	1	34
Total fluid[c] in first 6 hr (mL)			
Median (IQR)	1100 (600–1600)	1358 (1000–2069)	1250 (894–2000)
n	148	148	296
Intervention fluid in first 6 hr (mL/kg)			
Median (IQR	10 (6–18)	17.7 (12–26)	
Total IV fluid in first 6 hr (mL/kg)			
Median (IQR)	14.5 (8–23)	18.8 (13–29)	

IQR = interquartile range.
[a]IV fluid the participant was randomized.
[b]Any IV intervention fluid that participant was not randomized.
[c]All fluid including intervention, crossover, and maintenance.

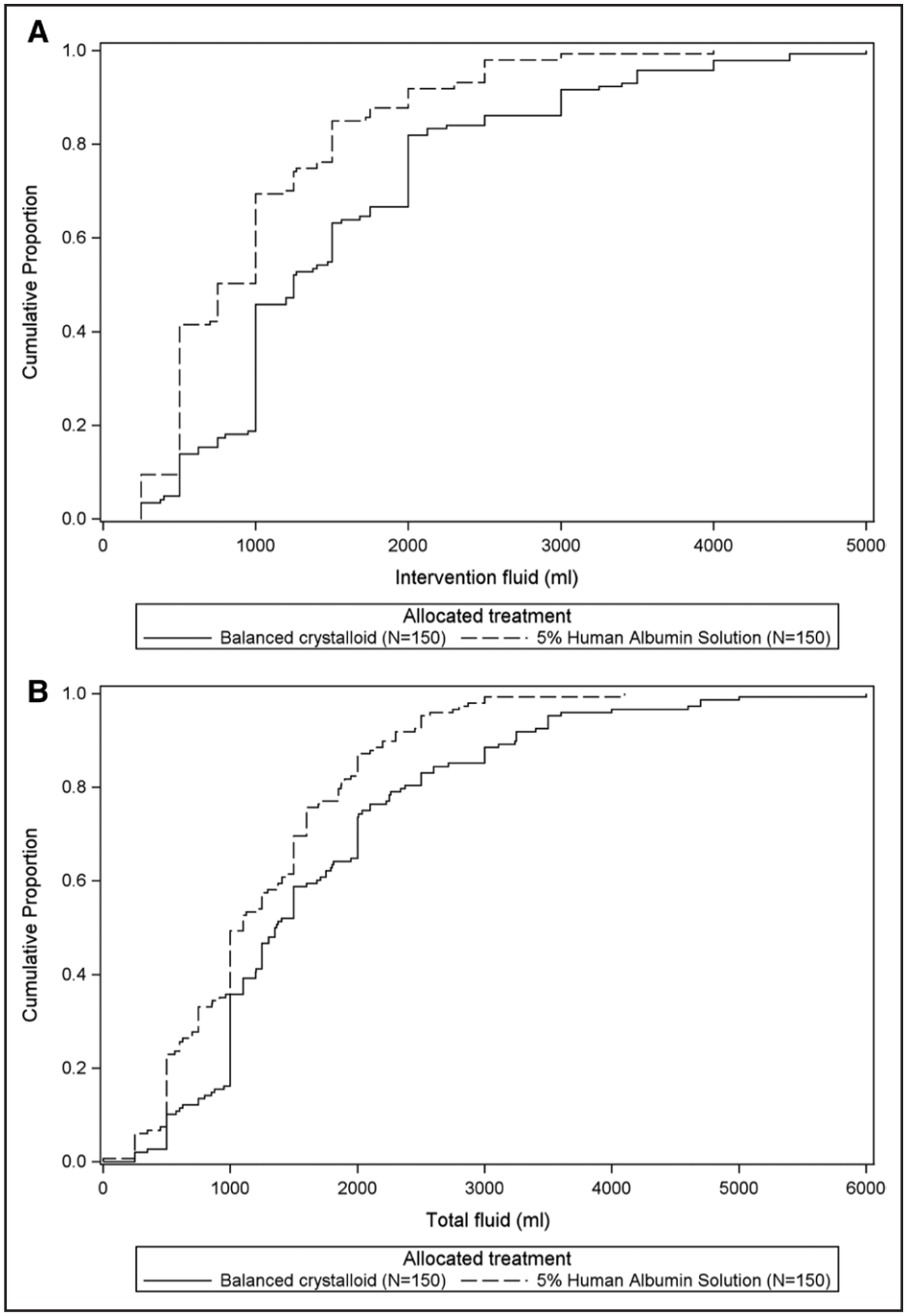

Figure 2. Cumulative distribution of IV fluid administration in first 6 hours after randomization. **A**, Allocated IV resuscitation fluid volume in first 6 hr after randomization. **B**, Total IV fluid volume in first 6 hr after randomization.

(25%) 5% HAS arm compared with 32 (21%) balanced crystalloid arm (Table 4).

There were 49 adverse events reported; 28 in the 5% HAS arm and 21 in the balanced crystalloid arm. Sixteen were defined as serious adverse events (**Supplementary Table S8**, http://links.lww.com/CCM/H557). None were defined as being intervention related.

HRQoL was measured by the EQ-5D-5L score. Greater than 90% of participants were able to report HRQoL at one or more of the timepoints. HRQoL between the two groups was similar at each time point (**Supplementary Table S9**, http://links.lww.com/CCM/H557).

DISCUSSION

We have demonstrated that it is feasible to perform an early IV fluid resuscitation trial comparing balanced crystalloid with 5% HAS, in patients with sepsis presenting to EDs. Our results highlight that approximately 25% of participants screened were recruited and the trial was delivered to time and target, suggesting feasibility of a definitive trial. Importantly, our screened/recruited rates are similar to many other trials in emergency care (17–19). In addition, 96% of randomized participants received their allocated trial fluid.

The ABC-Sepsis trial was designed to test feasibility and therefore was not powered to detect a significant difference in 30-day mortality, and other secondary outcomes, between intervention groups. The 30-day mortality was numerically, but not statistically, lower in the balanced crystalloid group compared with the 5% HAS group. Consistent with this signal, the 30-day mortality in prespecified subgroups and several secondary outcomes relating to critical care intervention were nonstatistically significantly lower in the balanced crystalloid group. Finally, recognized complications were also consistently lower in the balanced crystalloid arm. These findings are at odds to what may have been expected from previous reported literature in critical care trials (8–12) and contrary to mechanistic

TABLE 4.
Other Trial Outcomes

Outcomes	5% Human Albumin Solution	Balanced Crystalloid	All
Critical care interventions, *n* (%)			
IV vasopressors	18 (12.2)	12 (8.1)	30 (10.1)
Renal replacement therapy	1 (0.7)	2 (1.3)	3 (1.0)
Invasive ventilation	7 (4.7)	4 (2.7)	11 (3.7)
Complications, *n* (%)			
Acute kidney injury[a]	36 (24)	30 (20.1)	66 (22.1)
Pulmonary edema	22 (14.8)	11 (7.4)	33 (11.1)
Allergy and anaphylaxis	0 (0)	1 (0.7)	1 (0.3)
Hospital stay			
Length of hospital stay (d), median (IQR)	6 (3–13)	6 (3–15)	6 (3–14)
Readmission in 90 d, *n* (%)	38 (25)	32 (21)	70 (23)
ICU admission, *n* (%)	22 (15)	17 (11)	39 (13)
ICU length of stay (d), median (IQR)	5 (4–9)	4 (2–9)	5 (3–9)

IQR = interquartile range.

[a]Defined using National Institute of Health and Care Excellence (NICE) criteria (https://cks.nice.org.uk/acute-kidney-injury#!scenario).

data, which suggests that 5% HAS might be more protective compared with balanced crystalloid (20–22).

Based on our eligibility criteria, we anticipated our trial population would be older, multimorbid, have low critical care admission rates and a mortality rate of ~20% during index hospitalization (3, 4). Our population's mean age was 69 years, the 30-day mortality rate was 17.9%, participants had significant comorbidity, but only 13.9% were managed in critical care, despite 40% having a qSOFA of greater than or equal to 2 with half having a baseline lactate of greater than 2 mmol/L. The most common infection sites were respiratory and urinary tract, corresponding to previous emergency and critical care research (3, 4, 23). Trial eligibility criteria was pragmatic and recruitment early prior to microbiological confirmation of infection. Our pragmatic eligibility criteria also meant that patients recruited would meet the sepsis criteria, but not necessarily, the septic shock criteria defined within Sepsis-3 (24). In addition, frail and multimorbid patients may not receive advanced critical care, including vasopressors, because of decisions around the suitability of treatment escalation.

International guidelines suggest that patients with sepsis should receive ~30 mL/kg of IV crystalloid for fluid resuscitation in patients with sepsis-induced hypoperfusion or septic shock (5, 6). Historical literature suggests that approximately 1/3 of fluid volume is required when colloid is used in place of crystalloid to obtain a similar expansion in circulatory volume (25, 26). However, several large contemporary critical care trials, including the comparison of albumin and saline for resuscitation in the intensive care unit (SAFE) trial (8, 9), investigating the comparative effectiveness of colloids, have demonstrated lower comparative volume ratios of around 1–1.5. These trials are, in general, conducted beyond the initial resuscitation phase of care and delivered in a critical care rather than an emergency care population. We provided clinicians with pragmatic trial guidance on fluid volume aiming for resuscitation with up to 30 mL/kg for the balanced crystalloid arm and 10 mL/kg for the 5% HAS arm. Of note, these volumes were guided by clinical re-evaluation. Despite this, fluid volume separation between arms was lower with a ratio of 1–1.3 (5% HAS: crystalloid), similar to previous critical care trials (8, 9). Last, total volumes were lower than anticipated, which may reflect a clinical move toward lower fluid volumes during resuscitation or the trial population being less severely ill than those recruited to critical care trials or recent trials such as the crystalloid liberal or vasopressors early resuscitation in sepsis (CLOVERS) trial (23, 27–29).

There were some limitations in the design and conduct of the trial. The trial was open label and therefore at risk of bias related to a non-blinded design. The

trial protocol stipulated that participants should not receive crossover IV resuscitation fluid during the intervention period. Although there were no formal adherence limits, crossover was considerable in the 5% HAS arm, with 22% of participant receiving crossover fluid for resuscitation. We did not anticipate this level of crossover, and this may have impacted on the trial findings The crossover rate may reflect lack of clinician experience with the use of 5% HAS due to it not being routinely used in U.K. EDs (30, 31). We did not collect the reasons for non-adherence, and on reflection we should have done, as this would have helped the design of any subsequent trial. The trial included individuals for whom escalation to critical care may not have been of overall benefit, thereby limiting some management options. Although there was a requirement for IV fluid within 1 hour, this volume of resuscitation fluid may differ between sepsis, sepsis with evidence of hypoperfusion, and septic shock criteria (24). These reasons may have reduced the total volume of fluid given and diluted any potential benefits of 5% HAS as a volume sparing intervention. We only mandated the intervention for 6 hours, which may be too short a period for resuscitation to be completed, although additional volumes of fluid were relatively small between 6 and 24 hours. Although, we recruited ~25% of screened patients and recruited to target, we acknowledge that a lack of appropriately trained clinical staff was the main reason that eligible patients were not recruited. Potential solutions for this include increasing research staff availability, making trial training mandatory for all clinicians at recruiting sites and simplifying recruitment processes as much as possible.

The ABC-Sepsis trial has demonstrated the ability to recruit patients with sepsis to a U.K. ED IV fluid resuscitation trial. The trial recruited a population with a severity of illness and outcomes that were anticipated. We delivered the intervention with fluid volume separation between arms despite crossover of crystalloid administration into the 5% HAS arm. However, the mortality and clinical outcome findings from our feasibility work, along with the increased costs of 5% HAS, suggest that, although plausible, it is highly unlikely that any future superiority trial would demonstrate evidence of clinical or cost effectiveness of 5% HAS when compared with balanced crystalloid. Given this trial has demonstrated feasibility, future research may focus on the comparison of resuscitation fluids in specific sepsis phenotypes that may have the most to gain from use of volume sparing colloid.

CONCLUSIONS

The ABC-Sepsis trial has demonstrated the feasibility to successfully deliver a multicenter IV fluid resuscitation trial in U.K. EDs with recruitment on target and greater than 95% of participants receiving the intervention. There was separation in the primary outcome of 30-day mortality between arms with balanced crystalloid having a nonsignificantly lower mortality when compared with 5% HAS. Given these findings, a definitive superiority trial is likely to be deliverable but is unlikely to demonstrate that 5% HAS confers a survival advantage over balanced crystalloid that is clinically important.

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